ADVI

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Implications of the Inflation Reduction Act Price Setting Provisions on Post-approval New Uses for Biologics

Prepared for: The Pharmaceutical Research and Manufacturers of America

Executive Summary

Post-approval research and development (R&D) often involves evaluating the safety and efficacy of a U.S. Food and Drug Administration (FDA) approved medicine for new uses, including in the treatment of different conditions, different stages of disease, or different patient populations. Post-approval R&D is disincentivized under the Inflation Reduction Act's (IRA) Medicare Drug Price Negotiation Program (the Program). That is because under the law, medicines may be price set before they otherwise would have faced generic or biosimilar competition, thereby shortening the timeframe by which biopharmaceutical companies may feasibly invest in post-approval research.

Prior analyses examined the impact of the IRA's price setting provisions on post-approval research for small molecule drugs. This study describes the role of post-approval R&D in the lifecycle of biologic medicines, demonstrating that a large and diverse number of clinically important new uses are approved after a drug's initial approval by the FDA, often as many as 11 years later. Under the IRA, incentives to develop these new uses for biologic medicines will be significantly reduced. Yet, proposals to move up the price-setting timelines earlier in a biologic medicine's lifecycle may significantly worsen this effect. The findings presented here suggest that these impacts would be substantial.

Key findings include:

- Post-approval R&D on biologic medicines is an important source of new treatment options: Of the 32 biologic medicines approved from 2006 through 2012, representing 18% of total drug approvals, **72% received at least one additional approval after the initial FDA approval** (post-approval new uses).
    - **11% of post-approval new uses for biologic medicines were approved as many as 11 or more years after initial approval**. Moving forward, many of these new uses may no longer be pursued due to the shortened timelines under the IRA's price setting framework.
    - **59% of post-approval new uses for biologic medicines were approved 7 years or more after initial approval**, representing a majority of post-approval new uses. These findings demonstrate what may be lost if proposals to move up price setting timelines were implemented.
    - Post-approval new uses represent important advances for patients:
        - 53% of post-approval new uses were for new disease targets.

        - 22% of post-approval new uses were for new treatment populations.
        - Other important advances included new age groups (13%) and combination therapies (8**%**).
        - The most common therapeutic areas for post-approval new uses were rheumatology, oncology, and ophthalmology.
    - Impact on orphan drug development: 59% of medicines first approved as orphan drugs were awarded at least one additional post-approval new use.
- Spotlight on Cancer: Post-approval new uses are especially common with oncology medicines and represent important advances for cancer patients, with **57% of biologic cancer medicines receiving FDA approval for at least one new use**.
    - **6% of new uses were approved as many as 11 or more years after initial approval.**
    - **61% of new uses were approved 7 years or more after initial approval**, representing a majority of post-approval new uses**.**
    - Post-approval new uses represent important advances for cancer patients:
        - Nearly 40% of post-approval new uses awarded to biologic cancer medicines were for new combination therapies.
        - 33% of new uses were for a new disease target, generally a different type or subtype of cancer.
        - 11% of new uses were for earlier interventions in the progression of the cancer.

Background

Biologic medicines play a central role in the treatment of a wide range of diseases. Made from living cells through highly complex manufacturing processes, biologic medicines must be handled and administered under carefully monitored conditions. They are typically injected or infused, and most often administered in a doctor's office or in a hospital outpatient setting. Biologic medicines include a variety of products such as monoclonal antibodies, therapeutic proteins, vaccines, and cell and gene therapies—which may be used to treat a range of diseases including cancer, autoimmune disorders, as well as many chronic and rare conditions.

The IRA, which was signed into law in 2022, contains provisions that mandate the government select and set prices for eligible medicines, including biologics, covered by Medicare every year starting in 2023, with the first price controls going into effect in January 2026. According to these provisions and the Centers for Medicare and Medicaid Services' (CMS) implementation of the Program, the government can select eligible biologic medicines for price setting, if the medicine does not have a marketed biosimilar competitor. For biologics, this selection can come as early as eleven years after initial approval by the FDA, with the government set price going into effect two years later. Unfortunately, as the process imposed by the IRA for price-setting conflicts with other legal and regulatory frameworks governing biologics and the entry of biosimilars, it is likely that very few, or even zero, biologic medicines will be able to avoid price setting as a result of existing competition from biosimilars in the years ahead. Likewise, given this new prospect of price-setting occurring at 13 years after initial approval, biopharmaceutical companies will now have to consider the feasibility of investing in post-approval research later in a biologic medicine's life cycle.

Under the Biologics Price Competition and Innovation Act (BPCIA), enacted in 2009, 12 years after the first license of an existing "reference" biological product is the earliest point at which the FDA is permitted to approve a biosimilar to compete against the reference product. However, in practice there are often additional intellectual property protections, including patents, which may cover additional uses and offer protections beyond those twelve years. These intellectual property protections exist in part to not only incentivize R&D investment in new drugs but continued research on medicines that are already approved. Such incentives are needed because further clinical research after initial FDA approval to support approval for new uses in different diseases or treatment populations is very costly and uncertain. In fact, exploring a single new use of an already approved medicine can take an additional four years or

more of costly clinical trials, with no guarantee of success.[1]

By imposing price controls at year 13, biologic manufacturers will have to consider the feasibility of conducting post-approval R&D to explore new uses much earlier than they would have otherwise done so prior to the IRA. This is particularly true given the timelines required to conduct clinical trials and the practical need to ensure there will be sufficient time on the market to earn revenue on a new use before price-setting may occur. Realistically, biologic manufacturers will need to make these decisions no later than 6-7 years after initial approval, or realistically even earlier, given the range of financial factors that must be considered. These factors include the time and costs of expanding manufacturing capacity, which is a particular challenge associated with biologic medicines.

The importance of post-approval R&D for biologics

Post-approval R&D is an important source of new treatment options for patients with a wide range of diseases—including those commonly treated with biologic medicines. Biopharmaceutical companies conduct post-approval R&D to evaluate the safety and efficacy of medicines for new uses, including the treatment of different conditions, different stages of disease, or different patient populations. Post-approval R&D is vital to addressing unmet needs for patients, contributing to important advancements in the use of medicines and patient care. This is especially true in oncology, where post-approval research after a medicine is initially approved is essential to advancing new treatment options in different cancers or genetic subgroups, or in earlier stages of disease. It is also common among medicines to treat autoimmune conditions, where subsequent research often leads to approved uses in different, though related, autoimmune conditions that share disease pathways involved in inflammation.

To add to the understanding of the role of post-approval R&D in the drug development life cycle and how the IRA might disrupt this process in the future, this research brief quantifies the frequency, timing, and type of post-approval advances awarded to biologic medicines approved between 2006-2012. The findings suggest that policies such as the IRA, which undermine the longstanding biopharmaceutical timelines that have incentivized continued R&D investment in biologic medicines, could sharply reduce companies' investment in post-approval R&D, leading

[1] U.S. Food and Drug Administration. The Drug Development Process Step 3: Clinical Research. Published online January 8, 2018. Accessed November 27, 2024. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

to fewer new medical advances to address patient needs. Further, they suggest that policies to expand price setting earlier in a biologic medicine's life cycle may worsen this impact.

Methods

For this analysis, we used data from the FDA to compile a list of all biologic brand prescription medicines that received an initial FDA approval between January 1, 2006 and December 31, 2012.[2] We then analyzed the product labeling, FDA approval supplement categories, and approval types on the Drugs@FDA webpage[3] for each medicine to determine whether additional indications had been approved, and if so, the date when they were approved and included in the product labeling.

We defined a post-approval new use, for simplicity of analysis, as a single FDA-approved change to a product's labeling. It is possible that an indication defined this way can represent multiple advances.

To characterize the types of advances for patients that these post-approval new uses represented, we assigned each new use to one or more of the following categories, based on the information contained on the product label (categories are not mutually exclusive):

- *New disease target* – the medicine received approval to treat a new disease or organ system.
- *Earlier disease intervention* – the medicine was previously approved to treat a condition after other treatments had failed (later line of therapy) but is now approved for use in an earlier stage of disease or earlier in the treatment process, such as expanding from metastatic-only to all breast cancer.
- *Standalone therapy* – the medicine was previously approved for use in combination with other medicines for a particular condition but is now approved to be used to treat the condition on its own.

[2] Center for Drug Evaluation and Research. Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals. *FDA*. Published online March 21, 2023. Accessed May 9, 2023. https://www.fda.gov/drugs/drug-approvals-and-databases/compilation-cder-new-molecular-entity-nme-drug-and-new-biologic-approvals

[3] U.S. Food and Drug Administration. Approval Date(s) and History, Letters, Labels, Reviews. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (*Note: Some biologic drugs are also approved by the U.S. FDA's Office of Biologics Evaluation and Research. These drugs have not been included in the analysis).*

- *New combination therapy* – the medicine received a new indication for use in combination with another therapy it was not previously approved in combination with.
- *New age group* – the medicine received approval to treat a broader age range of patients than previously approved, such as expanding to treat a pediatric population.
- *Other population expansion* – the medicine received a post-approval new use for patients beyond the originally intended population, for a subgroup of that population.

We categorized medicines by therapeutic area based on the medicine's initial approval.

We generated descriptive statistics on this dataset to highlight the following:

- Number of medicines by number of post-approval indications, e.g., 0, 1-2, 3 or more.
- Number of medicines by timing of their post-approval indications, e.g., <5 years, 5-7 years, 7-11, or 11 or more years after the medicine's initial approval.
- Number of post-approval indications by therapeutic area. Therapeutic areas are mutually exclusive, but indications designated as treating rare disease may overlap with other listed therapeutic areas. For this analysis, the term "rare disease" is based on receipt of an orphan drug designation. Additionally, for simplicity of analysis, post-approval *new uses* are categorized as "rare" if the medicine's *initial* use carries an orphan designation from the FDA. Thus, a post-approval new use for a non-rare (non-orphan) condition may be categorized as rare, and a post-approval new use for a rare (orphan) condition may be categorized as non-rare, if the post-approval new use is for a different condition than the medicine's initial indication.
- Number of post-approval new uses by type of advance. Types of advances are not mutually exclusive.
- Similar statistics focused specifically on oncology medicines, for which post-approval advances may be particularly important.

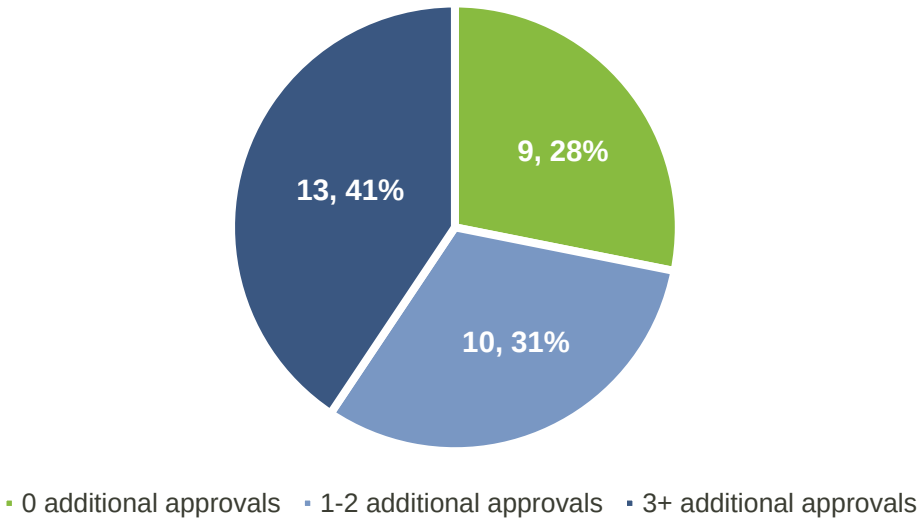
Results

From 2006-2012, a total of 32 biologics were approved by the FDA, representing 18% of total drug approvals. These medicines subsequently received approval for 82 additional post-approval new uses, representing 72% of the total approved uses for this medicine cohort. We note that this may understate the contribution of these post-approval new uses because we define a new indication as a single FDA-approved change to a product's labeling, and it is possible that an indication defined this way can represent multiple advances.

Post-approval indications

Continued development of biologics after their initial approval is common. 72% of biologics approved from 2006-2012 were awarded at least one post-approval new use, and 41% received three or more additional approvals (**Figure 1**).

Figure 1. **Medicines by number of post-approval new uses, for biologics receiving initial FDA approval between 2006-2012 (n=32 biologics)**



Of the 82 post-approval new uses developed for the biologic medicines in the sample, 59% of were awarded seven years or more after initial approval, and 11% were awarded after five years (**Figure 2**). Moreover, post-approval new uses were awarded steadily over many years after a medicine's initial approval, with new uses peaking 10 years following (**Figure 3**).

Figure 2. **Timing of post-approval new uses, for biologics receiving initial FDA approval between 2006-2012 (n=82 post-approval new uses)**

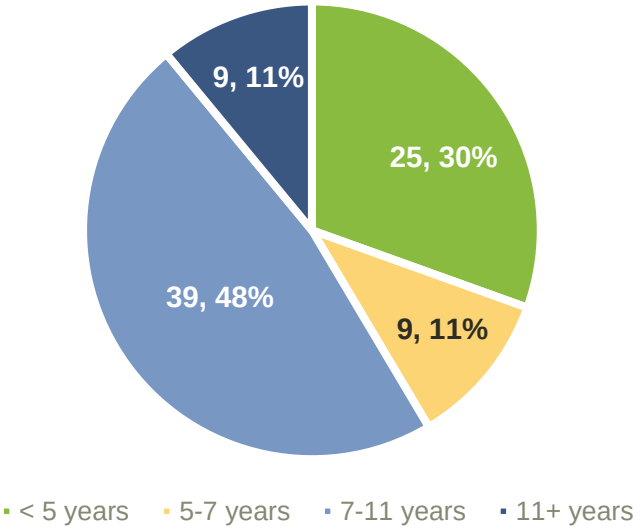
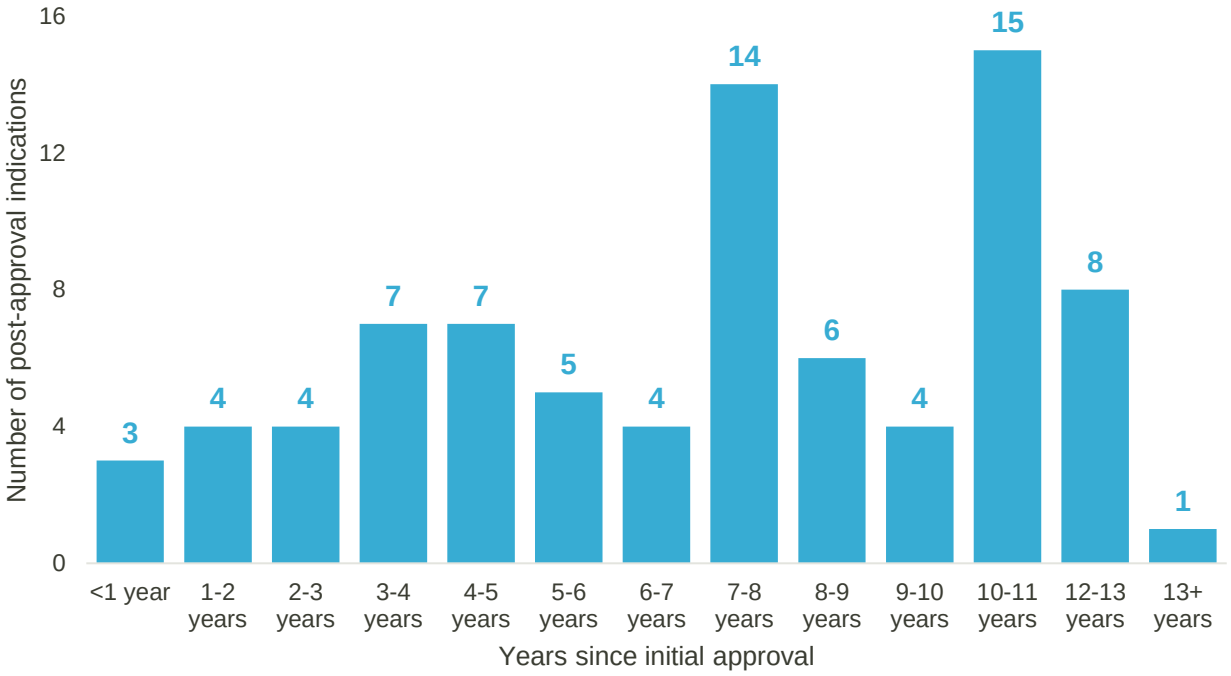


Figure 3. **Timing of post-approval new uses for biologics receiving initial FDA approval between 2006-2012 (n=82 post-approval new uses)***



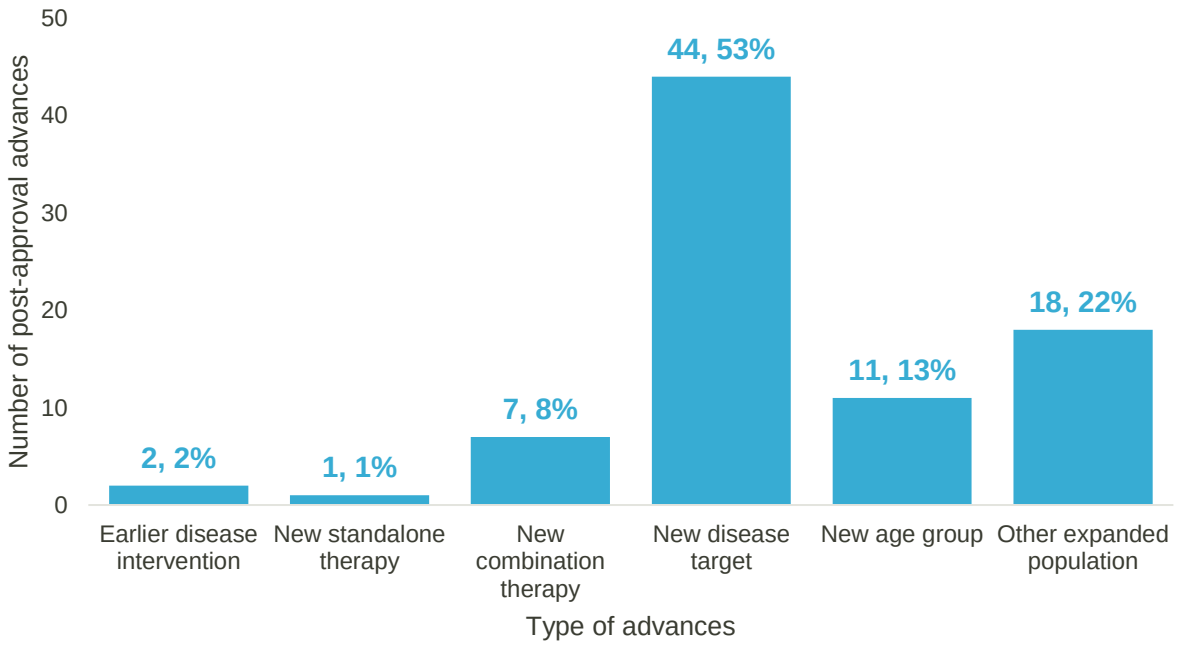
*Data are truncated until 2012. Additional approvals may extend beyond this timeframe.

Post-approval innovation by type of treatment advance

Post-approval new uses can represent a variety of different types of advances that expand the value of a medicine. These include expanding the use of the drug to treat different conditions, different stages of disease, or different patient populations (**see text box**).

Approximately half of post-approval indications for biologics awarded between 2006-2012 were awarded for new disease targets (**Figure 4**). This could include different subtypes of a disease (such as cancer), or entirely different conditions from the condition the medicine was originally approved to treat. 13% of post-approval indications expanded the use of the drug to different age groups (e.g., children), and 22% expanded the use to populations in ways unrelated to age, such as to patients with different comorbidities or patients with different treatment experience prior to taking the medicine.

Figure 4. **Type of treatment advances represented by post-approval new uses, for biologics receiving initial FDA approval between 2006-2012 (n=82 post-approval new uses)**



Examples of Post-approval Innovation

After receiving initial FDA approval for a medicine, a company often continues to develop the medicine to find new uses, expand treatment to more people, or to build evidence for how to use it more effectively. Below are some examples of ways companies have brought greater value to patients from their medicines through post-approval R&D on biologic medicines.

New disease targets. Post-approval research can demonstrate that a medicine approved for one condition is also effective for another condition.

> ***Example:*** *A medicine originally approved for adults with Crohn's disease receives additional post-approval indications for other autoimmune conditions—including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, and axial spondyloarthritis.*

Earlier disease intervention. Post-approval research can enable patient access to a therapy at an earlier stage of their disease, providing access earlier and when the patient is less severe.

> ***Example:*** *Another therapy originally approved for advanced melanoma is subsequently approved for use earlier in the treatment line or disease stage 12 additional times, not only in melanoma but many other forms of cancer.*

New standalone therapy. Post-approval research can help to reduce the number of medicines needed to treat a condition, avoiding associated adverse events, when efficacy of an adjunctive therapy is shown to be effective as a single treatment.

> ***Example:*** *A medicine that was initially approved for the treatment of a type of advanced colorectal cancer, along with chemotherapy, was subsequently approved for use without chemotherapy.*

New combination therapy. Post-approval research can demonstrate improved efficacy and safety when a medicine is used in combination with one or more other medicines. This is particularly true in cancer.

> ***Example:*** *An immunotherapy originally approved for advanced melanoma is subsequently approved in combination with another cancer immunotherapy in the same form of cancer as well as other types of kidney cancer, colorectal cancer, liver cancer, lung cancer, mesothelioma and esophageal cancer.*

New age group. Post-approval research can lead a medicine to be approved for additional age groups, often for populations with high unmet need such as pediatric patients, broadens the number of patients who can benefit from a medicine.

> ***Example:*** *A medicine originally approved for use in adults for the treatment of plaque psoriasis, and later in psoriatic arthritis, is subsequently approved for use in patients aged 6 years or older with pediatric forms of these illnesses.*

Other population expansion. Post-approval research can lead to a medicine being approved for patients beyond the originally intended population, for a subgroup of that population.

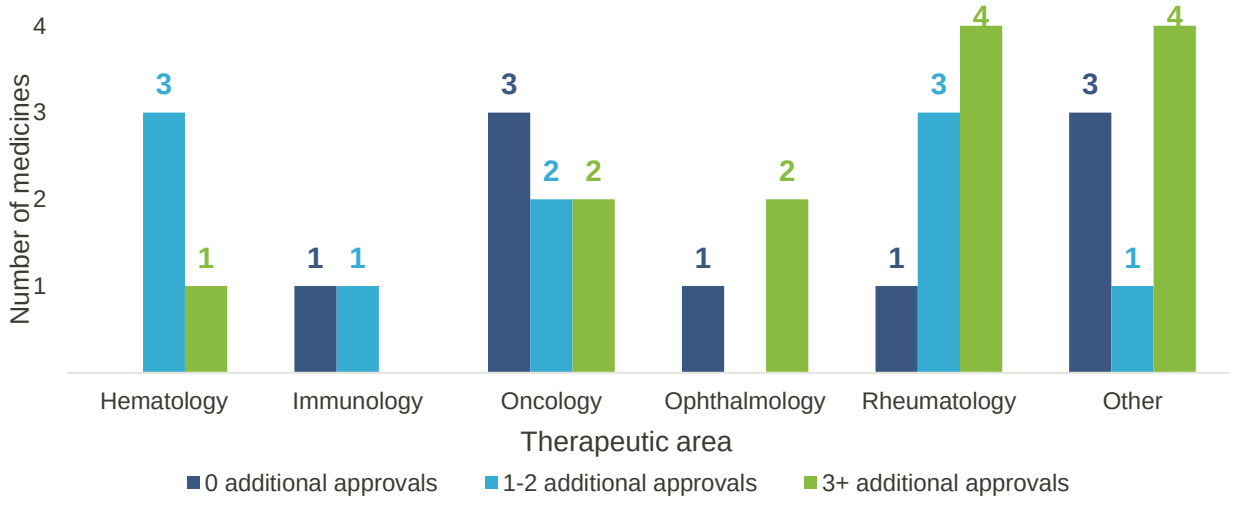
> ***Example:*** *A medicine initially approved for ALK-positive non-small cell lung cancer (NSCLC) that is locally advanced or that has spread to other parts of the body, is subsequently approved for advanced NSCLC whose tumors are ROS1-positive.*

Post-approval innovation by therapeutic area

As shown in **Figure 4**, post-approval indications for a medicine can be awarded in a different therapeutic area than the medicine's initial approval. For biologics approved between 2006 and 2012, 53% of post-approval new uses were approved for a different disease or disease subtype than the initial approval.

Other notable patterns emerge when we look at post-approval indications by therapeutic class (**Figure 5**). 100% of hematologic medicines and 89% of rheumatologic medicines were awarded at least one post-approval indication. Additionally, 59% of medicines originally approved as orphan drugs were awarded at least one post-approval new use.

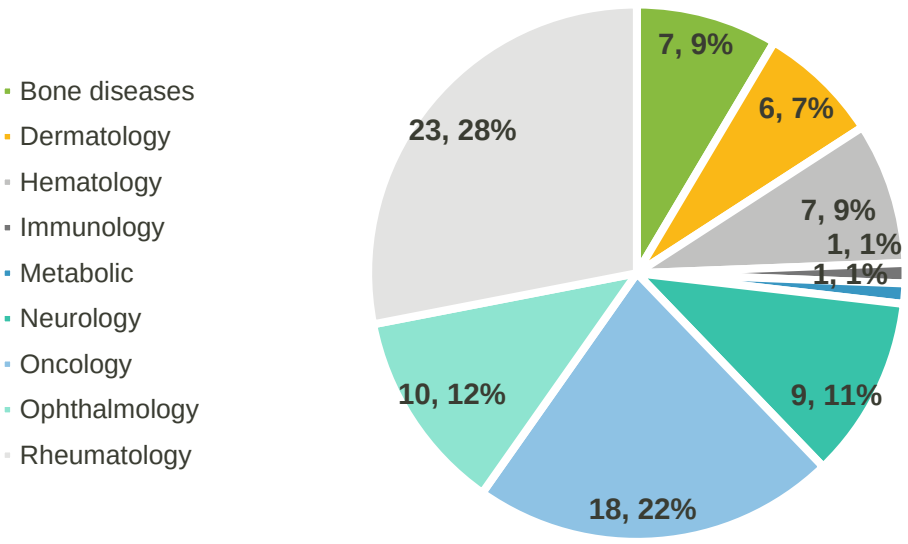
Figure 5. **Number of medicines with post-approval new use by select therapeutic area, for biologics receiving initial FDA approval between 2006-2012 (n=32 biologics)***



*Other: bone diseases, dermatology, metabolic, infection, neurology, nephrology, pulmonology.

The most common therapeutic areas for post-approval indications were rheumatology, oncology, and ophthalmology (**Figure 6**).

Figure 6. **Number of post-approval new uses by therapeutic area based on initial indications, for biologics receiving initial FDA approval between 2006-2012 (n=82 post-approval new uses)**



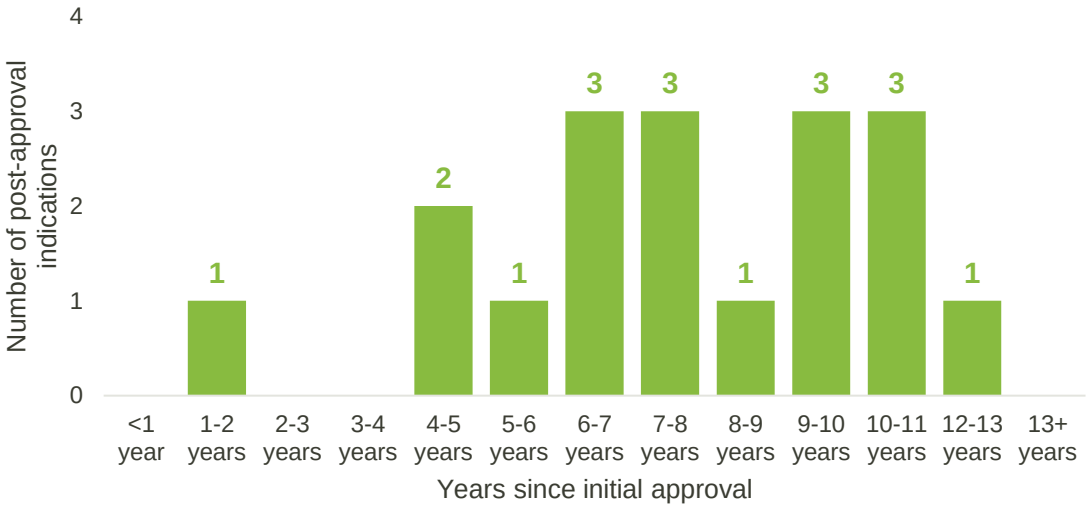
Note: Indications categorized by therapeutic area are based on the therapeutic area of the medicine's initial indication.

Spotlight on Cancer Medicines

Post-approval new uses were especially common within the oncology medicines in our sample. Of the 7 oncology biologic drugs approved from 2006 to 2012, 4 received at least one post-approval indication.

Notably, many of these post-approval indications were awarded after the biologic had been on the market for some time. Of the 18 post-approval new uses awarded to these cancer medicines, 61% were awarded seven years or more after the medicine's initial approval and 22% were awarded eleven or more years after initial approval (**Figure 7**).

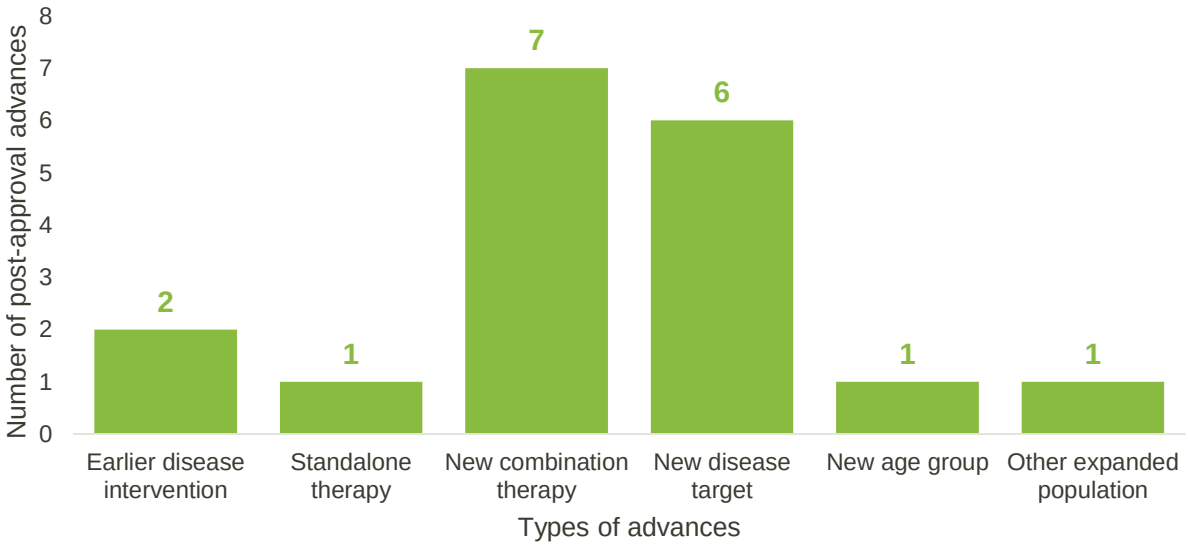
Figure 7*. Timing of all post-approval new uses for oncology biologics receiving initial FDA approval between 2006-2012 (n=18 post-approval new uses)



*Data are truncated.

The data further show that post-approval new uses for biologic cancer medicines represent important advances for cancer patients. Nearly 40% of these post-approval new uses were awarded for new combination therapies (**Figure 8**). 33% were for a new disease target, generally a different type or subtype of cancer. Importantly, 11% were awarded for earlier intervention in the progression of the cancer.

***Figure 8*. Type of advances represented by post-approval new uses for oncology biologics receiving initial FDA approval between 2006-2012 (n=18 post-approval new uses)**



Discussion

Our research shows that innovative biopharmaceutical companies often continue to invest in additional R&D after initial FDA approval of biologic medicines to assess the safety and efficacy of approved medicines for a variety of new uses, including new patient populations, additional stages of disease, and different conditions. 72% percent of the medicines in our sample received one or more post-approval new use in the years that followed initial approval. These new uses represent significant medical advancements that offer a wide range of conditions and patient populations new treatment options beyond the drugs' original studied use.

Notably, 100% of hematologic medicines and 59% of medicines originally approved as orphan drugs were awarded at least one post-approval new use. As more than 90% of rare diseases do not have a single FDA-approved treatment, and many deadly cancers (including rare cancers) still lack adequate treatment, post-approval R&D is critical to expanding treatment options for these patient populations.[4]

Under the IRA's Medicare Drug Price Negotiation Program, the government can select eligible biologic medicines for price-setting at eleven years after initial FDA approval, with the government set price going into effect two years later.[5] This timeline is often shorter than the timeframe that biopharmaceutical companies have relied on previously to incentivize the large and uncertain investments in R&D required to develop a medicine. In fact, in our analysis, 11% of post-approval new uses for biologic medicines were received as far as 11 years or later after initial approval. Unfortunately, the disincentives created by the IRA may cause many critical post-approval new uses for biologic medicines to never be realized.

The findings in this analysis not only illustrate how newly established government policies can jeopardize vital R&D initiatives after biologics are approved, but how policy proposals to expand the IRA and implement price setting even earlier in a medicine's product life cycle may worsen this impact. In fact, in our analysis, 59% of post-approval new uses for biologic medicines approved 7 or more years after initial approval, representing a majority of post-approval new uses. This finding illustrates what could be at stake if proposals to move up price setting timelines were implemented. Further, our findings suggest the impact in cancer would be more

[4] https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/
[5] Rep. Yarmuth JA [D K 3. H.R.5376 - 117th Congress (2021-2022): Inflation Reduction Act of 2022. Published August 16, 2022. http://www.congress.gov/

impactful, with 61% of post-approval new uses for biologic medicines approved 7 or more years after initial approval. Conducting R&D to meet unmet patient needs and further scientific progress requires substantial investment and time. Shortening the timeframe by which biologic manufacturers may conduct post-approval R&D even further than is currently required under the IRA, significantly undermines the motivation to invest in this essential R&D and puts the critical treatment advances they bring to patients at risk.